REMARKS

1. Status of the claimss

Claims 1-4, 6-7, 13-16,18-19, 25-26, 28-31,and 33-45 are currently pending. Claims 8-12 and 20-24 have been withdrawn. Claims 5, 17, 27, and 32 have been canceled. The rejections set forth in the Office Action are traversed by argument below.

2. Rejections under 35 U.S.C. § 103 (a)

As an initial matter, the Patent Office appears to have rejected the claims in part, in two separate rejections, rather than as a whole. As clearly stated in the M.P.E.P. 706.02 (j)

> *To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success.* ***Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.*** *The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).* [emphasis added]

Thus, it is impermissible to make separate rejections based upon only part of the claims as the references when combined must teach all of the claim limitations. In this case, however, the Office has issued a first rejection of all of the claims based upon Bankneider in view of York and DiPiro in relation to claim limitations regarding topical administration of aldose reductase inhibitor to the dermis and epidermis. The Office has then issued a second, separate rejection of all of the claims over York, in view of Guideline No. 38, Chen and DiPiro in relation to the claim limitations regarding comparing efficacy of compositions against other useful agents.

If the combination of Bankneider, York and DiPiro is used to argue obviousness with regards the claim limitations reciting topical administration of aldose reductase inhibitor to the dermis and epidermis, and the combination of York,

Guideline No. 38, Chen, and DiPiro is used to argue obviousness with regards the claim limitations reciting comparing wound healing in the presence of the compounds, then in order to properly assert a prima facie obviousness determination against each of the claims taken as a whole requires the combination of all the asserted references (Bankneider, York, DiPiro, Guideline No. 38, and Chen). Despite the clear instructions set forth in the MPEP, the Office has not asserted this rejection, and has not considered each claim as a whole. In an effort to expedite prosecution of these claims to allowance, however, Applicants will demonstrate in this response that even the combination of all five of these references still does not teach, suggest or make obvious all of the claim limitations of the independent claims. As a consequence, Applicants respectfully contend that the Office has not established a prima facie case of obviousness of independent claims 1, 13, 36, and 41 based on the cited references.

A. Claims 1-4, 6-7, 13-16, 18-19, 25-26, 28-31, 33-35 and 36-46 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Bankneider et al in view of York and DiPiro et al. The Applicants respectfully traverse the rejection.

According to M.P.E.P. 706.02 (j)

To establish a prima facie case of obviousness, ***three basic criteria must be met****. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success.* ***Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.*** *The teaching or suggestion to make the claimed combination and* ***the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure****. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).* [emphasis added]

As an initial matter, the Patent Office asserts in the instant Action that "the claims are directed to methods of identifying a compound for treatment of wounds to

dermis or epidermis of external body surface in a diabetic animal, *which also includes ophthalmic wounds*" (*emphasis added*). As Applicants have previously argued, this interpretation is incorrect as a matter of fact. First, the plain meaning of the claim language sets the metes and bounds of the claims as dermis or epidermis. There is no basis for including in this plain meaning wounds to the eye. This is evidenced by definitions and related diagrams of these terms from the "Medline Plus, Merriam Webster medical dictionary" and "Anatomy of the Eye": the skilled worker in the art would recognize that the eye is a specialized organ unique from the skin. The dictionary definition of the dermis is "the sensitive vascular inner mesodermic layer of the skin." The dictionary definition of "epidermis" is "the outer epithelial layer of the external integument of the animal body . . . that overlies the dermis." The dictionary definition of the eye is "an organ of sight, especially a nearly spherical hollow organ that is lined with a sensitive retina . . .." Applicant respectfully contends that there is no reference known to them that equates the eye with the skin, or teaches or suggests that the two organs are equivalent. None of the cited references make this claim. Applicants respectfully request, pursuant to 37 C.F.R. 1.104(d)(2), for any reference within the knowledge of the Examiner or any other Patent Office employee that would support the asserted equivalence of skin and the eye.

Moreover, the Patent Office itself distinguishes between preparations for use on the skin (Subclass 78.06) and ophthalmic preparations (Subclass 78.04).

Furthermore, as noted in the M.P.E.P. 2173.01:

> *A fundamental principle contained in 35 U.S.C. 112, second paragraph is that applicants are their own lexicographers. They can define in the claims what they regard as their invention essentially in whatever terms they choose so long as **>any special meaning assigned to a term is clearly set forth in the specification. See MPEP § 2111.01.< Applicant may use functional language, alternative expressions,* ***negative limitations****, or any style of expression or format of claim which makes clear the boundaries of the subject matter for which protection is sought. As noted by the court in In re Swinehart, 439 F.2d 210, 160 USPQ 226 (CCPA 1971), a claim may not be rejected solely because of the type of language used to define the subject matter for which patent protection is sought.*

Thus, so long as the use of a term is not contrary to the understanding of the worker skilled in the art (and for the reasons set forth above Applicants respectfully contend it does

not) an Applicant is permitted to delimit the use of a term such as dermis and epidermis as used in their claims. Applicants have clearly indicated in the application (Fig. 3 and Example 2) and in this current and consistently in previous responses that they do not consider wounds to the dermis/epidermis to include ophthalmic wounds and have limited the definition of dermal/epidermal to the skin. Applicants thus respectfully contend that when their claims state dermis and epidermis, that is precisely what they mean.

With respect to the references cited with particularity by the Patent Office, Applicants note the following:

Independent claims 1, 13, 36, and 41 all recite the following claim limitations:

a) producing ***a wound in the dermis or epidermis*** *of a diabetic animal;*

b) exposing ***the wound*** *to an aldose reductase inhibitor compound by topical application of the compound to* ***the wound****;...* [emphasis added]

None of the references cited by the Patent Office teach suggest or make obvious the noted claim limitations of independent claims 1, 13, 36, and 41.

The Patent Office cites Bankneider et al., which teaches improved wound healing by o*ral* or *parenteral* administration of an effective amount of tolrestat, an aldose reductase inhibitor (abstract and column 1, line 61). Thus, as noted by the Patent Office, Bankneider "fails to administer his aldose reductase inhibitor topically [to] the epidermis or dermis wound." However, the Patent Office then asserts later in the instant Action that

the wounds created by Bankneider is on the skin and thus on the dermis or epidermis of the subjects. Accordingly, the limitation of treating wounds to the dermis/epidermis is met by the prior art reference.

Applicants are not claiming merely making wounds in the skin of an experimental animal. Rather, their claims containing this limitation comprise a method for using such wounds to identify aldose reductase inhibitors that can improve wound healing through topical application. Bankneider teaches tolrestat administration systemically and parenterally, not topically; even the Office admits that Bankneider "fails to administer his aldose reductase inhibitor topically [to] the epidermis or dermis wound." It is well known to one of ordinary skill in the art that systemic (oral or

parenteral) administration of a compound is not equivalent to topical administration. It is further well known in the art that various medicaments containing the same active ingredient can have vastly different indications in the treatment of various disease states. Applicants thus respectfully contend that the Bankneider reference itself cannot render their pending claims obvious.

The Patent Office further cites the York reference which does not cure the deficiencies in Bankneider. York is directed to topical application (column 2, lines 10-11) of aldose reductase inhibitors to the eye to promote ocular wound healing, as noted in the Action: "York teaches…'these aldose reductase inhibitors can be applied topically to the eye or systemically.'" However, the York reference is silent as to topical administration of aldose reductase inhibitors to skin. Thus, the combination of the York reference and the Bankneider reference does not render Applicants' claims obvious, because there is no reason (other than the factually incorrect equivalence of the skin and the eye) the skilled worker would think that the effectiveness of ocular aldose reductase administration would have any significance for application of said aldose reductase inhibitors to skin.

The Office also errs in citing the York reference for teaching that "aldose reductase inhibitors are also suitable and effective in treatment through carrier systems appropriate for topical and ocular administration." This assertion appears to suggest that York distinguishes between topical and ocular administration. The Office directs Applicants to column 2, lines 1-67 of the reference as evidence for this assertion. Applicants respectfully note that nowhere in this cited section does York teach aldose reductase inhibitors for topical application to skin; the reference merely teaches that aldose reductase inhibitors could be administered "topically to the eye" (line 11); and recites "delivery of the involved aldose reductase inhibitors for corneal wound healing" (lines 27-28); "ocular administration" (line 31); "topical, ocular formulations" (line 45); and "ophthalmic indications" (line 67).

Finally, the Office also asserts that "the York reference teaches the equivalence of topical and systemic delivery;" without any citation to any specific portion of the reference. Even if this statement is correct, it is limited to the equivalence of topical and systemic administration to aldose reductase inhibitors to

the eye, and is irrelevant to any relationship between topical and systemic application to skin. Applicants are unaware of any reference that teaches such an equivalence for aldose reductase inhibitors, and respectfully request, pursuant to 37 C.F.R. 1.104(d)(2), for any reference within the knowledge of the Examiner or any other Patent Office employee that would support the asserted equivalence.

The parallels the Office attempts to draw in this regard are frankly contradicted by the teachings of the DiPiro reference, also cited by the Office. DiPiro states that "the eye, with its unique structure and function, is an extremely sensitive organ" (page 43, last paragraph) while "the skin provides an effective barrier to the usage of substances into as well as out of the body" (page 41, 2nd paragraph). Thus, even in a reference cited by the Office, significant differences are known to exist between the eye and the skin. These recognized differences support Applicants' position that the skilled worker would recognize that topical ophthalmic and topical skin administration are not equivalent and that neither is equivalent to systemic administration. Thus, York et al does not cure the deficiencies of Bankneider.

Turning again to the teachings of the DiPiro reference, the Office asserts this reference "show that it is well within the purview of one of ordinary skill in the art to prepare a topical or ophthalmic formulation, once in possession of the active ingredient." The Office further asserts that "converting a[n] ophthalmic to a topical composition is a matter of optimizing the carrier system." On the contrary, Applicants respectfully contend that DiPiro teaches that topical compositions for use on the skin and ocular compositions for use on the eye are not equivalents and, as discussed above, notes the unusual and specific nature of both ocular preparations and skin preparations. DiPiro states that "the eye, with its unique structure and function, is an extremely sensitive organ" (page 43, last paragraph) while "the skin provides an effective barrier to the usage of substances into as well as out of the body" (page 41, 2nd paragraph). Thus, even the art cited by the Office teaches that topical and ophthalmic preparations are not equivalents.

Furthermore, the ability to prepare a topical or ophthalmic composition once in possession of the active ingredient is not relevant to the pending claims. These claims are directed to a method for determining whether an aldose reductase

inhibitor can promote wound healing in skin. As set forth above, art showing such efficacy in ophthalmic preparations would not provide the skilled worker with a reasoned basis for such a method, without knowledge (not provided in any of the cited references) that aldose reductase inhibitors can promote wound healing in dermis or epidermis. The issue of whether one of skill in the art could make a topical preparation of an aldose reductase inhibitor is not relevant to methods for testing aldose reductase inhibitors for topical efficacy to skin; indeed, it puts the cart before the horse by presuming that the knowledge of aldose reductase inhibitor efficacy in ophthalmic wound healing is equivalent to knowledge of aldose reductase inhibitor efficacy in wound healing in dermis or epidermis. Since the art does not recognize this equivalence, this argument does not support the asserted prima facie obviousness determination.

In fact, there is evidence in the art that ophthalmic efficacy is not equivalent to efficacy in the dermis or epidermis. This is shown by the Sodi reference (Sodi et al.,(2003) J. Dermatol, 30(9):697-700), which demonstrates brimonidine tartate is an effective active ingredient for the treatment of glaucoma and ocular hypertension when administered opthalimically, but is ineffective when administered systemically and results in dermatologic irritation when administered to the skin.

Applicants respectfully contend that the teachings of the Bankneider reference are limited to efficacy of systemic administration of aldose reductase inhibitors, and that the teachings of the York reference are limited to the efficacy of ophthalmic administration of aldose reductase inhibitors. Neither of these references could be used to provide a logical reason why the skilled worker would seek to determine whether an aldose reductase inhibitor could be used topically to treat wounds in dermis or epidermis. These deficiencies are not cured by the teachings of the DiPiro reference, which is devoid of any specific teachings as to the efficacy of topical dermal and epidermal administration of aldose reductase inhibitors in wound healing. In fact, DiPiro teaches away from the idea that systemic, topical skin and topical ophthalmic compositions are equivalent and are similarly effective.

Thus, none of the references cited by the Patent Office alone or in combination teach, suggest or make obvious all the limitations of independent claims 1, 13, 36, and 41. Thus, the Patent Office has not established a *prima facie* case of obviousness of claims 1, 13, 36, and 41 based on the cited references. Rejected claims 2-4, 6-7, 14-16, 18-19, 25-26, 28-31, 33-35, 37-39, and 42-46 are dependent on the independent claims and share the above noted limitations and thus the references cited by the examiner also do not render these claims obvious. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

B. Claims 1-4, 6-7, 13-16, 18-19, 25-26, 28-31, 33-35 and 36-46 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over York in view of FDA Guideline No. 38, Chen and DiPiro et al. The Applicants respectfully traverse the rejection.

According to M.P.E.P. 706.02 (j)

> *To establish a prima facie case of obviousness,* ***three basic criteria must be met****. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success.* ***Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations****. The teaching or suggestion to make the claimed combination and* ***the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure****. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).* [emphasis added]

Independent claims 1, 13, 36, and 41 all recite the following claim limitations:

> a) *producing* ***a wound in the dermis or epidermis*** *of a diabetic animal;*
>
> b) *exposing* ***the wound*** *to an aldose reductase inhibitor compound by topical application of the compound to* ***the wound****;...* [emphasis added]

None of the references cited by the Patent Office teach suggest or make obvious the noted claim limitations of independent claims 1, 13, 36, and 41. In fact, the Patent Office has provided no direction, argument, or suggestion that the cited references teach at least these claim limitations of independent claims 1, 13, 36, and 41.

The Office cites York in this regard, and Applicants' contentions about the inappropriate citation of the York teachings set forth above are equally forceful with respect to this aspect of the asserted obviousness rejection.

The Office further cites Guideline No. 38, which is asserted to "to show the standard for assessing topical efficacy of candidate drugs." Guideline No. 38 is not asserted to teach "*producing* ***a wound in the dermis or epidermis*** *of a diabetic animal; exposing* ***the wound*** *to an aldose reductase inhibitor compound by topical application of the compound to* ***the wound***" as recited in the independent claims 1, 13, 36, and 41. Thus, Guideline No. 38 does not cure the deficiency of York, Bankneider, and DiPiro as addressed in section A above and, as stated in the MPEP, "*the prior art reference (or references when combined) must teach or suggest* ***all the claim limitations****.*"

The Office cites Chen as an example of Guideline No. 38. Chen is not asserted to teach "*producing* ***a wound in the dermis or epidermis*** *of a diabetic animal; exposing* ***the wound*** *to an aldose reductase inhibitor compound by topical application of the compound to* ***the wound***" as recited in the independent claims 1, 13, 36, and 41. Thus, Chen does not cure the deficiency of York, Bankneider, DiPiro, and Guideline No. 38 as addressed in section A above and, as stated in the MPEP, "*the prior art reference (or references when combined) must teach or suggest* ***all the claim limitations****.*"

Finally, the Office again cites DiPiro as showing "that it is well within the purview of one or ordinary skill in the art to prepare a topical or ophthalmic formulation, once in possession of the active ingredient." The reference has been addressed in detail in section A above. As previously noted, DiPiro, teaches that topical compositions for use on the skin and ocular compositions for use on the eye

are not equivalents and, notes the unusual and specific nature of both ocular preparations (page 43, last paragraph) and skin preparations (page 41 second paragraph). DiPiro does not provide any specific teachings as to the efficacy of topical dermal and epidermal administration of aldose reductase inhibitors in wound healing and thus does not cure the deficiency of Bankneider, York, Guideline No. 38 and Chen. In fact, DiPiro teaches away from the idea that systemic, topical skin and topical ophthalmic compositions are equivalents.

Thus, none of the references cited by the Patent Office alone or in combination teach, suggest or make obvious all the limitations of independent claims 1, 13, 36, and 41 as required by the M.P.E.P. Thus, the Patent Office has not established a *prima facie* case of obviousness of claims 1, 13, 36, and 41 based on the cited references. Rejected claims 2-4, 6-7, 14-16, 18-19, 25-26, 28-31, 33-35, 37-39, and 42-46 are dependent on the independent claims and share the above noted limitations and thus the references cited by the examiner also do not render these claims obvious. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

If Examiner Soroush believes it to be helpful, he is invited to contact the undersigned representative by telephone at 312-913-0001.

Respectfully submitted,
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Dated: February 4, 2008

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